DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 22 1999

Chih-Ming Chen, Ph.D., President
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Re: Docket No. 98P-0145/CP1 & SUP1

Dear Dr. Chen:

This responds to your citizen petition, dated February 26, 1998, supplement, dated September 9, 1998, and comments to the docket requesting that the Food and Drug Administration (FDA) act as follows:

1. Clarify the requirements for demonstrating in vivo bioequivalence to a controlled release reference drug product designed to manifest a distinct two-peak pharmacokinetic profile which subsequently results in a distinct and measurable two-valley pharmacodynamic profile.

2. Require a generic drug product to match the distinct two-peak pharmacokinetic profile of the reference drug unless exceptional circumstances are shown, specifically that the failure to match the profile of each peak is (i) intentional and is appropriately reflected in the labeling, (ii) is not essential to the attainment and maintenance of effective body drug concentrations on chronic use, and (iii) is considered medically insignificant to the "switchability" of patients from the reference to the generic drug product and vice versa.

3. Refrain from approving any abbreviated new drug application (ANDA) for a controlled release drug product for which adequate in vivo bioequivalence data do not demonstrate that the sponsor's drug matches the two-peak pharmacokinetic profile of the reference drug, unless the ANDA demonstrates that all of the foregoing exceptional circumstances are shown.

4. Refrain from approving any ANDA for Cardizem CD, a controlled release product specially designed with a two pulse dissolution (in vitro) release rate that manifests a two-peak pharmacokinetic (in vivo) profile which subsequently results in a two-valley pharmacodynamic profile, unless pharmacokinetic data demonstrate that the ANDA sponsor's drug matches the two-peak pharmacokinetic profile for the reference drug or the ANDA demonstrates, through clinical data, that the

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difference in profiles is not medically significant and all of the other exceptional circumstances are shown.

In reaching its decision, FDA has considered information in the petition, the supplement, comments submitted to the FDA regarding the petition (including the comments submitted by Andrx Pharmaceuticals, Inc. (Andrx)), and other information available to the Agency. For the reasons set forth below, the petition is denied in part and granted in part.

I. Diltiazem Hydrochloride

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist) used in the treatment of hypertension and angina. Hoechst Marion Roussel, Inc., (HMR) manufactures three types of diltiazem hydrochloride under approved new drug applications (NDAs): Cardizem immediate release (IR) tablets, Cardizem SR sustained (extended) release capsules, and Cardizem CD, extended release capsules. Cardizem tablets, administered in divided doses three or four times daily, were approved by FDA on November 5, 1982, for the management of chronic stable angina and angina due to coronary artery spasm. Cardizem SR capsules, administered twice daily, were approved on January 23, 1989, for the treatment of hypertension. Cardizem CD capsules, administered once a day, were approved on December 27, 1991, for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. The formulation of Cardizem CD combines fast and slow dissolving beads, resulting in a two-peak pharmacokinetic profile in the majority of healthy subjects receiving the drug product.

II. Statutory and Regulatory Basis for Approval of ANDAs for Controlled Release Drug Products

A. Statutory Basis

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the current abbreviated new drug application (ANDA) approval process.[1] Approval of a generic drug requires documentation that the drug is bioequivalent to the innovator drug (reference listed drug) that was approved under an NDA.[2]

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[1] The goal of the amendments was to allow more expeditious approval and marketing of lower-priced generic versions of previously approved innovator drugs.

[2] A generic drug that establishes bioequivalence, as well as pharmaceutical equivalence, is rated as therapeutically equivalent to the reference drug in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the *Orange Book*.

B. Regulatory Basis

Under the Hatch-Waxman Amendments, the Agency issued regulations that govern bioequivalence determinations.[3] The regulations at 21 CFR 320.23(b) state:

> Two products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.

The Agency also issued regulations[4] governing bioavailability studies that specifically address how to study bioavailability of controlled release formulations of drug products. [5]

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[3] See also 21 U.S.C. § 355(j)(8)(B)-(C). Prior to enactment of the Food and Drug Administration Modernization Act of 1997 (Modernization Act), bioequivalence was described at section 505(j)(7)(B)-(C) of the Act. The Modernization Act added new provisions to section 505(j) that resulted in a renumbering of the sections.

[4] At 21 CFR 320.25, the regulations on guidelines for the conduct of an in vivo bioavailability study, paragraph (f) focuses on bioavailability for controlled release formulations. Section 320.25(f)(1) states:

> (1) The purpose of an in vivo bioavailability study involving a drug product for which a controlled release claim is made is to determine if all the following conditions are met: (i) The drug product meets the controlled release claims made for it. (ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping. (iii) The drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application. (iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

[5] See also 21 CFR 320.27. These regulations describe guidelines for the design of a multiple-dose in vivo bioavailability study. Section 320.27(a)(3) includes the following statements:

> A multiple-dose study may be required to determine the bioavailability of a drug product in the following circumstances: (i) There is a difference in the rate of absorption but not in the extent of absorption. (ii) There is excessive variability in bioavailability from subject to subject. (iii) The concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in the blood resulting from a single dose is too low for accurate determination by the analytical method. (iv) The drug product is a controlled release dosage form.

C. Relevant Guidance Documents

The Agency published two documents based on these regulations that serve as guidance to generic applicants submitting ANDAs for controlled release products. The first, a 1984 guidance entitled *Division of Biopharmaceutics Guidelines for the Evaluation of Controlled Release Drug Product,* provides recommendations to sponsors for the types of clinical safety and efficacy and **bioavailability** studies to support an application for a first entry[6] NDA controlled (extended) release dosage form.[7]

The second guidance, a companion to the first, was published in 1993 and is entitled *Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence Testing and In Vitro Dissolution Testing.* This guidance provides recommendations about studies to document **bioequivalence** between a generic extended-release product and the corresponding extended-release innovator drug.[8] While the regulations at §§ 320.25 and 320.27, as well as the 1984 guidance, focus on documentation of **bioavailability**, the 1993 guidance extends the general approaches to the documentation of **bioequivalence**.

III. Bioequivalence Requirements for Controlled Release Drug Products

A. FDA's current in vivo bioequivalence requirements are adequate to ensure the bioequivalence of drug products manifesting a two-peak pharmacokinetic profile.

You state that the 1993 guidance does not currently require that "the pharmacokinetic release profile of the reference product be matched by the generic drug, or if the profile is not matched, that the generic drug's pharmacokinetics be displayed in the bioequivalence study report with sufficient precision that FDA can determine whether the difference in bioavailability is 'medically insignificant'" (Petition at 4). Because of this alleged omission you contend that the Agency's 1993 guidance with respect to controlled release products fails to meet its stated goal of ensuring that clinical performance is equivalent between the generic and the reference listed product following single doses and dosing to steady state (Petition at 4). This failure to meet its goal, you maintain, results specifically from the method of blood sample collection the guidance recommends, as well as the type of calculations used to measure pharmacokinetic parameters.

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[6] Controlled release dosage forms for previously approved immediate release drug products and controlled release dosage forms not intended to be interchanged with other controlled release dosage forms.

[7] The guidance also recommends three types of bioavailability studies: (1) a single-dose fasting study; (2) a food-effects study; and (3) a steady-state study.

[8] The guidance recommends a single-dose fasting study, a food-effects study, and a steady-state study to assess bioequivalence of extended release drug products.

You assert that a difference in the pharmacokinetic profiles of generic and reference drugs is likely to be most significant when a reference drug has a multiple-peak profile correlating to specific pharmacodynamic effects (Petition at 5). Accordingly, you ask the agency to revise its bioequivalence testing requirements to require that the ANDA applicant match the pharmacokinetic release profile of the drug it references or to provide data to establish that failure to match the profile is intentional and medically insignificant to generic substitution for the reference listed product.

FDA believes that the current bioequivalence testing measures, requiring equivalence of plasma concentrations expressed as AUC and Cmax, are appropriate criteria for testing the bioequivalence of controlled release drug products. These measures are most likely to predict overall effect and to protect against an excessive response at peak. The importance of differences in rate of absorption or pharmacokinetic profile will be assessed on a case-by-case basis; if differences in overall profiles are shown to be medically significant, two products would not be considered bioequivalent. However, the Agency does not agree that it should routinely require ANDA applicants to match multiple-peak reference drug profiles or to demonstrate that failure of their drug products to match the profiles is medically insignificant.[9]

B. ANDA applicants are not required to match two-peak pharmacokinetic profiles of reference drugs unless the Agency determines that the two-peak profile is medically significant.

You maintain that the pharmacokinetic profile of an ANDA applicant's drug product must match a reference drug's multiple-peak profile (Petition at 10). You further state that if the plasma profile of an ANDA applicant's drug product does not match the multiple-peak pharmacokinetic profile, the applicant must supply FDA with sufficient data for the Agency to determine if the failure to match is medically significant (Petition at 10). Therefore, you ask the Agency to presume the pharmacokinetic profile of the reference drug is medically significant even in the absence of clinical data to support this conclusion and to place the burden on an ANDA applicant to establish the medical insignificance of any variation between the ANDA drug plasma profile and that of the reference listed drug product. The Agency declines to place such a burden on ANDA applicants.

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[9] We also note that we have no evidence of an apparent benefit from a formulation that produces a two-peak plasma profile that merits special effort to distinguish it from a formulation with more consistent release. Indeed, as a general matter, it is usually preferable for a product to provide consistent release over the dosing interval. A major potential advantage of a controlled release formulation is avoidance of the peaks and troughs associated with multiple administrations of immediate release products. To the extent that a formulation provides plasma concentrations that achieve a plateau with minimal fluctuation, and smooths the peaks and valleys of a two-peak plasma profile, it may be considered an improvement over the formulation that causes two peaks in plasma concentrations, although with generally similar effects.

For reasons given above, the multiple-peak profile does not ordinarily appear to constitute a difference to be preserved, particularly for an antihypertensive agent where a consistent 24-hour effect is desirable. The Agency recognizes that it is possible that some multiple-peak drugs could have medically significant differences from their single-peak counterparts. When the multiple-peak plasma profile appears medically significant, this likely will be made apparent to the Agency during the NDA approval process and will also be reflected in the reference listed drug's labeling.[10]

If the Agency determines that the reference listed drug's safety and/or efficacy is affected by a distinct and consistently reproducible second peak in the plasma profile, and that this peak therefore is medically significant, an ANDA applicant will be required to match the plasma profile of the reference listed drug prior to approval of the generic drug product. Under these conditions, FDA would use its authority to require a pharmacokinetic profile match for specific drugs on a case-by-case basis. (See 57 FR 17950 at 17974, April 28,1992, response to comments 90 and 91.) In the absence of such a determination by the Agency, a pharmacokinetic profile match will not be required.

In the absence of data showing the contrary, temporary fluctuations in blood pressure from baseline because of multiple peaks in the plasma profile would not be considered medically significant. Development of data to conclude that a second peak is medically significant would require a clinical outcome study enrolling very large numbers of patients.[11] In the absence of NDA or other data establishing medical significance of a second peak in the drug's plasma profile, it is unreasonable for the Agency to require ANDA applicants to conduct studies to establish bioequivalence of their generic product to the reference drug by demonstrating the medical insignificance of any difference in rate of absorption.

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[10] As you note in your petition, the Agency has previously approved applications for two-peak plasma profile reference drugs. You specifically cite FDA approvals of Adalat CC (nifedipine) Extended Release Tablets (Bayer Corporation), Claritin-D (loratadine/pseudoephedrine sulfate) 12-hour and 24-hour Extended Release Tablets (Schering Corporation), and Cardizem CD (diltiazem HCl) Capsules (HMR). The information that you cite related to the pharmacokinetic profiles of both Adalat CC and Claritin-D is gleaned from the *labeling* of those drug products. The two peak plasma profile of Cardizem CD, by contrast, is not referred to in its labeling.

You also cite the Agency's response to a 1993 citizen petition requesting a suitability determination regarding indomethacin 75-mg constant release tablets as additional support for your petition. You state that although the petition did not address a multiple-peak issue, it did involve the importance of controlled release mechanisms and corresponding drug delivery. FDA's response to that petition, however, is not germane to the issues raised in your petition. While the response did address the release mechanism of the innovator drug, the release mechanism for indomethacin is not the same as that of Cardizem CD, and indomethacin is an entirely different drug product from diltiazem HCl with different clinical indications. Accordingly, conclusions drawn regarding indomethacin have no bearing on the agency's approach in this case.

[11] For example, a study to compare the safety and efficacy of two diltiazem HCl controlled release products, as proposed by Dr. William White, Professor of Medicine at the University of Connecticut School of Medicine, in a comment to your petition, would require the enrollment of tens of thousands of patients.

Moreover, as explained in section IV below, in this case the Agency does not find that Cardizem CD's two-peak plasma profile is consistently reproducible or medically significant. Because of this finding, and this conclusion that two-peak pharmacokinetic profiles of other drug products are not necessarily medically significant, the Agency declines to develop a guidance requiring ANDA applicants to match the pharmacokinetic profile of reference listed drugs in every case. Instead, it will continue to determine medical significance of multi-peak plasma profiles on a case by case basis.

C. The potential use of systemic exposure metrics as an alternative approach to bioequivalence determinations is limited.

While you recognize that the Agency does not require generic drug products to match the shape of the reference listed drug's pharmacokinetic profile, you assert that the Agency should do so when the shape correlates to the drug's pharmacodynamic profile. You cite an article by Thomas N. Tozer et al.[12] to support the claim that shape or systemic exposure metrics may be important for establishing bioequivalence (Supplement at 1).

The Agency is considering whether new shape metrics are appropriate in some instances to better define systemic exposure patterns of certain drug products. Even if the Agency adopts the use of new metrics in the future, however, their use will be limited. FDA would apply the shape metrics concept only after the pioneer or other manufacturer submitted compelling evidence documenting that a particular exposure pattern provided added therapeutic value[13] and that the benefit could be reproduced consistently in patients administered the drug product. The Agency will not adopt additional shape metrics where no clinical safety and efficacy data establish that the exposure pattern is medically significant. Nor will the Agency encourage ANDA applicants to produce controlled release drug products that do not achieve and maintain an adequate blood level of the active moiety/ingredient throughout the dosing interval unless compelling evidence demonstrates that this results in a significant clinical difference.

As described more fully below, the Agency does not find that Cardizem CD's exposure pattern has been shown to be medically significant. Therefore, the Agency will not use new shape metrics to evaluate bioequivalence for ANDA applications referencing Cardizem CD.

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[12] "Absorption Rate vs. Exposure: Which Is More Useful for Bioequivalence Testing?" *Pharmaceutical Research*, vol. 13, p. 453, 1996.

[13] For example, a rapid release product may be preferable to a conventional release drug when rapid onset of action is desirable, as with orally administered analgesics. On the other hand, a slower release formulation may be important to reduce toxicity associated with rapid input.

IV. Cardizem CD's Pharmacokinetic Profile

Given the absence of evidence establishing the medical significance of Cardizem CD's two-peak pharmacokinetic profile, FDA will not require ANDA applicants to demonstrate that their drug products match the two-peak plasma profile, or to demonstrate that any difference in profiles between the reference and generic drugs is medically insignificant.

A. Cardizem CD does not possess an intentional, distinct, consistent, and reproducible two-peak pharmacokinetic profile.

In your petition you describe Cardizem CD as possessing "two peaks in the pharmacokinetic curve [that] are controlled, equal sized, reproducible and distinctly separated from each other" (Petition at 9). You also state that the Medical Review demonstrates a "clear-cut correlation between the two peak plasma concentrations at hours 6 and 14 post dose and ambulatory blood pressure minima (i.e., 'valleys') at 7-8 and 15-16 hours post dose, respectively" (Petition at 6). Finally you state that the "peaks and trough of the release curve and the pharmacodynamic effects on blood pressure persist during chronic dosing" (Petition at 9).

Cardizem CD, however, possesses a formulation that combines fast and slow dissolving beads resulting in a *variable* two-peak pharmacokinetic profile, rather than one that is intentional, distinct, consistent, and reproducible. The variability in profile results from the innovator's use of a variable ratio of fast to slow dissolving beads in the drug product. The innovator developed a multiple-level C correlation between the in vitro dissolution and the in vivo plasma profiles to vary the ratio of fast to slow dissolving beads. The innovator developed this correlation to match a certain desired Cmax and AUC. From the data submitted in the application and the sponsor's representations to the advisory committee, it appears that the innovator never intended to correlate the overall in vitro dissolution performance with the second peak in the pharmacokinetic profile, instead focusing on the Cmax and AUC parameters. The innovator's failure to consider the second peak in the development and testing of the drug product illustrates that it did not deem the second peak clinically important or necessary to achieve the desired in vivo performance.

The bioavailability and bioequivalence studies submitted by the innovator to the Agency demonstrate the variability in Cardizem CD's pharmacokinetic profile. The studies reveal that the second peak of Cardizem CD may occur anywhere from 10 to 16 hours post dose. Additionally, some studies exhibit an intralot variability in the mean concentration of the second peak exceeding 15 percent. Moreover, a second peak was not even observed in one study. These data demonstrate that the innovator did not design the dosage form to meet a particular target value for the second peak and that the Agency did not believe a particular value for the second peak was essential to the drug's therapeutic effectiveness or safety.

Data submitted by Andrx in ANDA 74-852 similarly demonstrate the variability of the two-peak plasma profile. The multiple-dose study conducted by Andrx establishes the presence of two-

peak plasma profiles in only 50 percent of the test subjects administered Andrx's generic formulation of diltiazem HCl. The data further show two peaks in the plasma profiles of only 40 percent of the test subjects given Cardizem CD in the multiple-dose study. These data suggest that neither the innovator nor Andrx could meet bioequivalence guidelines if they were required to match a second plasma profile peak as you request in the petition. With respect to the multiple-dose study in ANDA 74-852, the Agency welcomes comments from Andrx explaining the absence of consistently present two-peak plasma profiles in either their product or Cardizem CD.

B. *No clinical benefit is associated with the second peak in Cardizem CD's pharmacokinetic profile.*

You contend in your petition that differences in the rate of absorption of diltiazem HCl controlled release products, reflected in variances in the pharmacokinetic profiles of the drug, cannot be viewed as medically insignificant (Petition at 10). You do not, however, provide any data to establish that the second peak in the plasma profile of Cardizem CD is clinically significant.

Data in the innovator's NDA also do not establish the clinical importance of Cardizem CD's second peak in the pharmacokinetic profile. The innovator did not submit any evidence that the second peak is necessary from the pharmacodynamic and clinical perspective. In fact, according to the Medical Review of Clinical Data of NDA 20-062, Cardizem CD, dated Feb. 5, 1991 (Medical Review), the second peak appears to contribute strongly to the variability in Cardizem CD's therapeutic effect. Controlled release formulations generally aim to minimize fluctuations in drug plasma levels, not to emphasize them. The Agency would expect a sponsor to identify any clinically beneficial effects associated with significant fluctuations should such therapeutically positive effects occur. The absence of data submitted by the innovator indicates that the innovator was unaware of or unable to establish any intended or unintended beneficial effects of the varying pharmacokinetic profile.

The Agency similarly notes that unlike the labeling for Adalat CC and Claritin-D, the innovator labeling for Cardizem CD does not include information related to the two-peak plasma profile phenomenon. It is true that the medical review briefly comments that data in one protocol demonstrate a double-peak plasma concentration and drop in blood pressure apparently correlating with the second peak. The review then notes that the "variability in therapeutic effect of Diltiazem QD[14] apparent during 24-hour monitoring of diastolic blood pressure seems to be related to the release system of the drug" (Medical Review at 101). However, neither the Medical Review nor the labeling ascribe a clinical importance to this finding. The absence of comment in the labeling implies that the innovator and the Agency did not find the two-peak plasma profile to be medically significant.

[14] The NDA for Cardizem CD was initially filed under the proprietary name Cardizem QD.

Not surprisingly, the innovator failed to mention the two-peak plasma profile of Cardizem CD in several other instances. For example, although the innovator conducted bioequivalence studies to compare the product with a competing controlled release formulation,[15] the innovator never raised the two-peak plasma profile issue when evaluating the studies. Along these lines, the innovator did not include a statement in NDA 20-062 that the presence of a two-peak plasma profile was medically advantageous or that the second peak's absence would lead to adverse effects. Similarly, the innovator did not include information about the unique plasma profile in corresponding promotional efforts. This failure to mention Cardizem CD's two-peak pharmacokinetic profile suggests that the innovator was not aware of any purported clinical benefits associated with the second peak and did not deem the second peak necessary to achieve the desirable in vivo performance.

With respect to Cardizem CD, the Agency notes the two-peak pharmacokinetic profile does not adequately indicate clinically meaningful fluctuations in blood pressure at steady state. If, as you state in your petition, there are significant fluctuations in blood pressure at steady state with Cardizem CD, this would suggest that the drug product does not adequately maintain blood pressure over the 24-hour period expected of controlled release product. The approval of Cardizem CD for marketing demonstrates the Agency determined that the two-peak plasma profile phenomenon was not significant enough to preclude approval of the drug.

By finding that Cardizem CD's second peak has not been shown to be clinically significant based on the available data, the Agency does not foreclose the possibility that an ANDA applicant or other firm could establish that a clinical benefit is associated with the two-peak pharmacokinetic profile of Cardizem CD. The Agency welcomes additional data in this regard and will reevaluate its position should such data warrant this course of action.

C. A two-peak pharmacokinetic profile in a one-dose-daily controlled release diltiazem formulation is not necessary for the maintenance of lowered blood pressure.

The Agency has approved two one-dose-daily controlled release formulations of diltiazem HCl in addition to Cardizem CD. Those drugs, Dilacor XR and Tiazac,[16] do not exhibit the phenomenon of two-peak plasma profiles in either the in vitro dissolution or the in vivo plasma concentrations. Yet both drugs were approved as safe and effective as one-dose-daily anti-hypertensives. Their approvals demonstrate that a second peak in a pharmacokinetic profile of a controlled release diltiazem formulation has not been found to be necessary to maintain a blood pressure lowering effect over 24 hours.

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[15] Dilacor XR, sponsored by Watson Laboratories, Inc.

[16] Sponsored by Forest Pharmaceuticals, Inc.

D. The evidence does not establish that the two-peak pharmacokinetic profile of Cardizem CD is medically significant.

You state that Dr. Bertram Pitt, Professor of Internal Medicine at the University of Michigan School of Medicine, recommends that the Agency require that ANDA applicants conduct clinical outcome tests assessing pharmacodynamic factors to establish the medical insignificance of a generic drug formulation with a plasma profile that does not match that of Cardizem CD. You discuss Dr. Pitt's opinion that safety issues could arise when a patient is administered a different formulation of the diltiazem HCl one-dose-daily product (Petition at 10-11).

While Dr. Pitt expresses concerns based on his considerable clinical experience and background, he does not support his comments with any data. The Agency cannot accept his conclusions in the absence of data to support them. Additionally, because Cardizem CD does not have a narrow therapeutic index, concerns regarding safety related to an ANDA applicant's failure to match the two-peak pharmacokinetic profile are minimized. In the absence of data to support safety concerns, the Agency will not require an ANDA applicant to establish the medical insignificance of any difference in plasma profile between the applicant's drug product and that of Cardizem CD.

You may, of course, submit additional data to the Agency to establish that safety issues exist when an ANDA applicant fails to match the two-peak plasma profile of Cardizem CD. The Agency solicits and welcomes any additional information that Andrx or any other firm may provide.

V. Pharmacodynamic measurements not necessary criteria for bioequivalence testing

You state that "the kinetics and blood pressure effects of Cardizem CD are closely correlated," and assert that, therefore, "a diltiazem product with a distinctly different pharmacokinetic profile from Cardizem CD is not likely to be pharmacodynamically equivalent to Cardizem CD." You quote Dr. Pitt for the proposition that a difference in the rate of absorption of two diltiazem hydrochloride preparations may be deemed medically insignificant if the preparations "produce similar blood pressure and heart rate profiles over 24 hours (the dosing period) on ambulatory blood pressure monitoring" (Petition at 9-10). You also ask the Agency to require an ANDA applicant referencing Cardizem CD either to match the two-peak plasma profile or "to demonstrate, through clinical data, that the difference in profiles is not medically significant" (Petition at 2). Through this request, you effectively ask the Agency to require an ANDA applicant that does not match Cardizem CD's two-peak plasma profile to conduct clinical studies assessing the pharmacodynamic impact of the variation in plasma profiles.

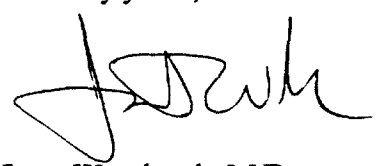
The Agency declines to require that ANDA applicants conduct clinical trials using pharmacodynamic data (systolic and diastolic blood pressure data) as a measurement of bioequivalence for antihypertensive drugs. Bioequivalence criteria for antihypertensive drugs that depend on pharmacodynamic measurements could not be sufficiently precise because of intrasubject and intersubject variability with blood pressure measurements. The Agency division

responsible for evaluating antihypertensive drugs, the Division of Cardio-Renal Drug Products, does not require sponsors of NDAs for those drugs to perform pharmacodynamic measurements for the determination of bioequivalence when comparing batch formulations of the sponsor's drug product. Similarly, the Agency will not impose such a requirement on generic drug manufacturers. Pharmacokinetic, rather than pharmacodynamic, criteria will continue to be the standard for bioequivalence determinations related to Cardizem CD.

VI. Conclusion

The Agency will not routinely require ANDA applicants for innovator drugs with multiple-peak plasma profiles to match those profiles. Your request that the Agency revise its bioequivalence guidance to require plasma profile matches for drug products with multiple-peak plasma profiles unless the ANDA applicant can establish, in addition to other exceptional circumstances, the medical insignificance of any variation in the profile is therefore denied. Your request that the Agency refrain from approving any ANDA for any controlled release product that fails to match the innovator's multiple-peak plasma profile is similarly denied. The Agency also denies your request to refrain from approving any ANDA for Cardizem CD unless the ANDA applicant matches the innovator's two-peak plasma profile. Your petition is granted, however, to the limited extent that the Agency will continue on a case by case basis to require ANDA applicants to match an innovator's medically significant plasma peak profile and will consider providing more specific guidance about how the Agency will determine when an ANDA applicant must match a multiple-peak plasma profile of an innovator's controlled release drug product.

Sincerely yours,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research